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EXAMINER
KERR, KATHLEEN M

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 07/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/752,957	SHIUAN, DAVID	
	Examiner	Art Unit	
	Kathleen M Kerr	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *1-7,15 and 16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Application Status

1. In response to the previous Office action, a restriction requirement (Paper No. 11, mailed on March 26, 2003), Applicants filed an election and amendment received on April 25, 2003 (Paper No. 12). Said amendment amended Claim 8. Thus, Claims 1-16 are pending in the instant Office action.

Election

2. Applicant's election with traverse of Group II, Claims 8-14, in Paper No. 12 is acknowledged. The traversal is on the ground(s) that the Groups are not distinct and that their examination together would not be burdensome. Applicants argue that the Groups are not distinct because the alternative method cited by the Examiner for use of the product "simply re-states a major aspect of the method of Group II...to obtain yeast with high biotin productivity". This is not found persuasive because the alternate method expressed by the Examiner was to produce biotin synthase, an enzyme, not to produce biotin. Moreover, the plasmid product can be used for additional methods, such as hybridization assays to isolate new biotin synthase enzymes. Thus, the product can be used in at least two distinct methods of using the product. Applicants also argue, "a search of a yeast expression plasmid will necessarily bring up reference to the yeast expressing it and how the yeast were transformed"; the Examiner disagrees. There is no requirement in the art, either the published journals or the patent literature, to express all plasmids produced. Particularly in the patent literature, additional class/subclasses would have to be searched rendering the additional claims "burdensome". Moreover, to anticipate the

method claims, numerous steps must be taught by the art – steps that may or may not be taught by the art anticipating the product claims. If the plasmids were examined first and found allowable, all methods using said plasmids could be rejoined pursuant to the procedures set forth in the Official Gazette notice dated March 26, 1996 (1184 O.G. 86; see also M.P.E.P. § 821.04, *In re* Ochiai, and *In re* Brouwer). However, Applicants have elected to prosecute the methods, and just because the methods are allowable does NOT mean that the products are allowable.

Concerning Applicants' traversal of the distinctness of Group III, the additional method step of making biotin in these methods renders the claims distinct and requiring a different search. Particularly in the patent literature, additional class/subclasses would have to be searched rendering the additional claims "burdensome".

The requirement is still deemed proper and is therefore made FINAL.

Priority

3. The instant application is granted the benefit of priority for the foreign application 89120972 filed in Taiwan on October 7, 2000 as requested in the declaration.

Receipt is acknowledged of papers submitted under 35 U.S.C. § 119(a)-(d), which papers have been placed of record in the file. Said papers are not in English and cannot be used to assess the earliest effective filing date of the claimed subject matter. Thus, a priority date of January 2, 2001, the filing date of the U.S. application, will be considered for prior art in the instant Office action. If priority to October 7, 2000 is needed to overcome art rejections in the instant Office action, Applicants must file a certified translation of the priority document.

Information Disclosure Statement

4. The information disclosure statement filed on January 29, 2001 (Paper No. 2) has been reviewed, and its references have been considered as shown by the Examiner's initials next to each citation on the attached copy.

Compliance with the Sequence Rules

5. Applicants filed a sequence listing on September 25, 2002 (Paper No. 8) containing a single SEQ ID NO in computer readable form and paper copy. Said listing has been entered. This sequence listing is based on a sequence in the specification on pages 10-11. The Examiner notes that in the sequence listing filing, Applicants call the sequence "amended". The Examiner requests confirmation that the sequence filing in the listing in Paper No. 8 is identical to the sequence found in the originally filed specification on pages 10-11.

6. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to **fully** comply with the requirements of 37 C.F.R. § 1.821 through 1.825; Applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990).

a) On page 9, line 29, two DNA primers are disclosed without benefit of SEQ ID NO.

b) On page 10, line 10, two DNA primers are disclosed without benefit of SEQ ID NO.

If the noted sequences are in the sequence listing as filed, Applicants must amend the specification to identify the sequences appropriately by SEQ ID NO. If the noted sequences are not in the sequence listing as filed, Applicants must provide (1) a substitute copy of the sequence

listing in both computer readable form (CRF) and paper copy, (2) an amendment directing its entry into the specification, (3) a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. § 1.821 (e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d), and (4) any amendment to the specification to identify the sequences appropriately by SEQ ID NO.

Objections to the Specification

7. The specification is objected to because the title is not descriptive. A new title is required that is clearly indicative of the invention to which the elected claims are drawn (see M.P.E.P. § 606.01). The Examiner suggests the following new title:

---Methods for Preparing Yeast with High Biotin Productivity Using Integrated Plasmids encoding Biotin Synthase---

8. In the specification, the Abstract is objected to for not completely describing the disclosed subject matter (see M.P.E.P. § 608.01(b)). It is noted that in many databases and in foreign countries, the Abstract is crucial in defining the disclosed subject matter, thus, its completeness is essential. The Examiner suggests the inclusion of the invention of the *Candida utilis* biotin synthase gene, bioB, as well as its integration into the *C. utilis* genome. Other embodiments include *Saccharomyces cerevisiae* integrating plasmids. Species embodiments are crucial in understanding the specifics of what the disclosure has to offer. Correction is required.

9. The specification is objected to for the following inconsistencies and/or confusing subject matter:

a) On page 3, line 11, it is unclear why "biotindase" is boxed.
b) On page 7, line 17, SEQ ID NO:1 only describes the *C. utilis* sequence; this is not clear from the language, which includes the *S. cerevisiae* sequence.
c) On page 12, lines 13-14, references to an incomplete 204 sequence and a complete 233 sequence are unclear since the 1188 base pair DNA disclosed as SEQ ID NO:1 encodes a 396 amino acid protein.
d) On page 14, lines 24-26, the reference to 8.2 ng/ml of biotin produced in the wild-type is unclear considering that the Table on page 15 shows the wild type producing 26 ng/ml.
e) On page 15, in Table 1, the OD_{600nm} of m21-105 appears to be a typographical error since it is 100-fold different from other numbers in the table.
f) On page 15, in Table 1, the ng/ml of m9-101 in YPD(CHY) appears to be a typographical error since it is 10-fold different from other numbers in the table.

Correction and/or explanation are required.

Objections to the Claims

10. Claims 8-14 are objected to for depending on a non-elected claim, Claim 1. All the limitations of Claim 1 must be amended into Claim 8. Correction is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 8-14 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "high" is a relative term, which renders the claim indefinite. The term "high" is not defined by the claim, the specification does not provide a standard for ascertaining

the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention. Clarification is required.

12. Claims 8-14 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "integrated" in Claim 8, and as the claims depend from Claim 1, is confusing as to whether the term is used as an adjective merely describing the plasmid or as a verb describing what the plasmid is required to do in the method. Moreover, the appropriate term would be an integrating plasmid, particularly because once the plasmid has integrated it is no longer a plasmid. The term "integrating" is a term used in the art (see Stearns *et al.* and YIp or yeast integrating plasmid – Stearns *et al.* Manipulating yeast genome using plasmid vectors. Methods in Enzymology (1990) 185:280-297). Correction and/or clarification are required.

13. Claims 8-14 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "assistant DNA sequence for the integration of said plasmid into a host genome" is unclear; the Examiner cannot find the term "assistant DNA" as a term of art of defined in the specification. A good reference is the enclosed Stearns *et al.* who teach the use of URA3 and HIS3 markers for integration. The Examiner suggests deleting the term "assistant" from the phrase.

14. Claims 9-10 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as

the invention. The phrase "derived from" is unclear as to its metes and bounds. In today's recombinant technology, numerous mutations to a native *S. cerevisiae* or *C. utilis* sequence can be performed wherein the resulting sequence is still "derived from" *S. cerevisiae* or *C. utilis*. Is the intended limitation ---native to--- to indicate a naturally occurring sequence? It is unclear and clarification and/or amendment are required.

15. Claim 10 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The antecedent basis of "gene of *Candida utilis*" is unclear based on the above rejection concerning the term "derived from". Clarification is required.

16. Claim 11 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "NsiI-BamHI 18s rDNA" is unclear as to its exact make-up. The rDNA of yeast are distinct from each other and are large repeating units of DNA. Is this fragment a single, specific fragment? Or are there many embodiments? What are those embodiments? The scope and definition of the term are unclear. The Examiner notes that URA3 and HIS3 DNA, also found in the claim, are used routinely in the yeast integrating plasmid art.

17. Claim 12 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "cycloheximide-resistant gene" is unclear. Genetic markers in the art are typically used; these are genes that encode proteins that provide resistance by virtue of

modifying the antibiotic, sequestering the antibiotic and/or removing the antibiotic from the cell. In other words, the gene is not "resistant" but provides ---resistance---. Correction and/or clarification are required.

18. Claim 13 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The promoters "pL41" and "pADH1" are unclear as to their exact nature based on the abbreviations used herein. The L41 gene of *C. utilis* and the ADH1 gene of *S. cerevisiae* are clear in the art; moreover, the promoters of these genes are also well defined. However, the "p" abbreviation renders the claims unclear since, in the art, a preceding "p" indicated a plasmid name. Clarification of these terms is required.

19. Claim 14 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear exactly how the phrase "useful as feed additives, food additives, or cosmetics" limits the subject matter of the parent claim. What are the additional requirements on the yeast used in the methods. Clarification is required.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

20. Claims 8-10 and 14 are rejected under 35 U.S.C. § 102(b) as being anticipated by Pearson *et al.* (GB 2216530A, see PTO-892) as evidenced by Stearns *et al.* (see PTO-892). The instant claims are drawn to methods for making yeast that make biotin using an integrating plasmid that contains a biotin synthase gene, DNA integration sequences, a promoter, and a selection marker, wherein the plasmid is constructed, linearized, and transformed into the yeast. No real limitations on the biotin synthase gene are considered in the instant claims based on the rejections under 35 U.S.C. § 112, second paragraph above.

Pearson *et al.* teach expression of the *E. coli* biotin synthase, bioB, in yeast (see pages 1-3) to produce biotin (see page 4, lines 27-31); the *E. coli* bioB gene can be "derived from" the *S. cerevisiae* or *C. utilis* bioB genes by virtue of numerous mutations, substitutions, and/or deletions. Pearson *et al.* teach introducing bioB into the yeast host cell by integration (see page 2, lines 5-6 and page 8, lines 34-36). Pearson *et al.* also teach using appropriate promoters (see page 5, lines 27-32) and genetic markers (page 6, lines 23-27). The steps of constructing the integrating plasmid to include DNA integrating sequences (such as HIS3 and URA3), linearizing it, and transforming the yeast host cell are all inherent features of the integration taught by Pearson *et al.* as noted in Stearns *et al.* (see page 287, Fig. 2 legend).

The Examiner notes that Claim 11 is omitted from the instant rejection because the HIS3 and URA3 sequences taught by Stearns *et al.* are not from *C. utilis*, nor are they inherent features of all integrating protocols. Furthermore, with respect to Claims 12 and 13, particular resistance markers and/or promoters are not inherent features of all integrating protocols.

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

21. Claims 8-10 and 14 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Pearson *et al.* in view of Stearns *et al.* and Hong *et al.* (GenBank Accession Number AF212161, publicly available December 7, 2000). The instant claims are drawn to an interpreted species of Claims 9 and 10 drawn to methods for making yeast that make biotin using an integrating plasmid that contains specifically a *C. utilis* biotin synthase gene in addition to DNA integration sequences, a promoter, and a selection marker, wherein the plasmid is constructed, linearized, and transformed into the yeast.

Pearson *et al.* teach expression of the *E. coli* biotin synthase, bioB, in yeast (see pages 1-3). Pearson *et al.* also teach the use of functional equivalents of bioB (see page 5, lines 5-14). Pearson *et al.* teach introducing bioB into the host cell by integration (see page 2, lines 5-6 and page 8, lines 34-36). Pearson *et al.* also teach using appropriate promoters (see page 5, lines 27-32) and genetic markers (page 6, lines 23-27). The steps of constructing the integrating plasmid, linearizing it, and transforming the yeast host cell are all inherent features of the integration taught by Pearson *et al.* as noted in Stearns *et al.* (see page 287, Fig. 2 legend).

Pearson *et al.* do not teach using the functional equivalent of the bioB gene encoding biotin synthase that is from *C. utilis*.

Hong *et al.* teach the *C. utilis* biotin synthase gene equivalent to bioB in *E. coli* (see definition).

It would have been obvious to one of ordinary skill in the art to replace the *E. coli* biotin synthase gene used in the methods of Pearson *et al.* with the *C. utilis* biotin synthase gene taught by Hong *et al.* because Pearson *et al.* expressly teach the use of functional equivalents and Hong *et al.* identify their sequence as a functional equivalent. One would have been motivated to combine the above references to practice the methods using yeast and integrating plasmids containing the *C. utilis* biotin synthase gene because functional equivalents are described as useful variations of the invention of Pearson *et al.* One would have had a reasonable expectation of success that when the *C. utilis* biotin synthase gene was integrated into yeast host genome, the yeast host cell would have produced biotin because yeast naturally produce biotin and introduction of a biotin synthase gene would not have been reasonably expected to inhibit said production.

22. Claims 8-10 and 14 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Pearson *et al.* in view of Stearns *et al.* and Zhang *et al.* (The gene for biotin synthase from *Saccharomyces cerevisiae*: cloning, sequencing, and complementation of *Escherichia* coli strains lacking biotin synthase. Arch Biochem Biophys (1994) 309(1): 29-35). The instant claims are drawn to an interpreted species of Claim 9 drawn to methods for making yeast that make biotin using an integrating plasmid that contains specifically a *S. cerevisiae* biotin synthase gene in addition to DNA integration sequences, a promoter, and a selection marker, wherein the plasmid is constructed, linearized, and transformed into the yeast.

Pearson *et al.* teach expression of the *E. coli* biotin synthase, bioB, in yeast (see pages 1-3). Pearson *et al.* also teach the use of functional equivalents of bioB (see page 5, lines 5-14). Pearson *et al.* teach introducing bioB into the host cell by integration (see page 2, lines 5-6 and page 8, lines 34-36). Pearson *et al.* also teach using appropriate promoters (see page 5, lines 27-32) and genetic markers (page 6, lines 23-27). The steps of constructing the integrating plasmid, linearizing it, and transforming the yeast host cell are all inherent features of the integration taught by Pearson *et al.* as noted in Stearns *et al.* (see page 287, Fig. 2 legend).

Pearson *et al.* do not teach using the functional equivalent of the bioB gene encoding biotin synthase that is from *S. cerevisiae.*

Zhang *et al.* teach the *S. cerevisiae* biotin synthase gene equivalent to bioB in *E. coli* (see definition).

It would have been obvious to one of ordinary skill in the art to replace the *E. coli* biotin synthase gene used by Pearson *et al.* with the *S. cerevisiae* biotin synthase gene taught by Zhang *et al.* because Pearson *et al.* expressly teach the use of functional equivalents and Zhang *et al.* identify their sequence as a functional equivalent. One would have been motivated to combine the above references to practice methods using yeast and integrating plasmids containing the *S. cerevisiae* biotin synthase gene because functional equivalents are described as useful variations of the invention of Pearson *et al.* One would have had a reasonable expectation of success that when the *S. cerevisiae* biotin synthase gene was integrated into a yeast host genome, the yeast host cell would have produced biotin because yeast naturally produce biotin and introduction of a biotin synthase gene would not have reasonably been expected to inhibit said production.

23. Claim 11 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Pearson *et al.* in view of Stearns *et al.* and Rodriguez *et al.* (Development of an integrative DNA transformation system for the yeast *Candida utilis*. FEMS Microbiol Lett (1998) 165(2): 335-340). The instant claims are drawn to methods for making yeast that make biotin using an integrating plasmid that contains a biotin synthase gene, DNA integration sequence URA3 from *C. utilis*, a promoter, and a selection marker, wherein the plasmid is constructed, linearized, and transformed into the yeast.

Pearson *et al.* teach expression of the *E. coli* biotin synthase, bioB, in yeast (see pages 1-3). Pearson *et al.* teach introducing bioB into the host cell by integration (see page 2, lines 5-6 and page 8, lines 34-36). Pearson *et al.* also teach using appropriate promoters (see page 5, lines 27-32) and genetic markers (page 6, lines 23-27). The steps of constructing the integrating plasmid, linearizing it, and transforming the yeast host cell are all inherent features of the integration taught by Pearson *et al.* as noted in Stearns *et al.* (see page 287, Fig. 2 legend).

Pearson *et al.* do not teach using the specific DNA integration sequence from *C. utilis* that is URA3 DNA.

Rodriguez *et al.* teach integrative transformation of *C. utilis* using *C. utilis* URA3 DNA (see Abstract).

It would have been obvious to one of ordinary skill in the art to use *C. utilis* URA3 DNA as a means of the integration by Pearson *et al.* in view of Stearns *et al.* because Stearns *et al.* specifically teach the use of HIS3 and URA3 DNA from the host yeast to be transformed (see page 286, Table II). One would have been motivated to combine the above references to practice methods using yeast and integrating plasmids containing a *C. utilis* URA3 integration sequence

because the use of all yeasts in the methods is taught by Pearson *et al.* and the teachings of Rodriguez *et al.* enable the use of *C. utilis* as the yeast and teach how *C. utilis* is a useful industrial microorganism (see page 335). One would have had a reasonable expectation of success that when a *C. utilis* URA3 DNA integration sequence was used in the integrating plasmid, successfully transformed yeast host cells would have contained integrated biotin synthase and would have produced biotin because Rodriguez *et al* demonstrate the effectiveness of the integrative system and because *C. utilis* naturally produce biotin and introduction of a biotin synthase gene would not have reasonably been expected to inhibit said production.

24. Claim 12 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Pearson *et al.* in view of Stearns *et al.* and Kondo *et al.* (see IDS). The instant claims are drawn to methods for making yeast that make biotin using an integrating plasmid that contains a biotin synthase gene, DNA integration sequences, a promoter, and a cycloheximide-resistance selection marker, wherein the plasmid is constructed, linearized, and transformed into the yeast.

Pearson *et al.* teach expression of the *E. coli* biotin synthase, bioB, in yeast (see pages 1-3). Pearson *et al.* teach introducing bioB into the host cell by integration (see page 2, lines 5-6 and page 8, lines 34-36). Pearson *et al.* also teach using appropriate promoters (see page 5, lines 27-32) and genetic markers (page 6, lines 23-27). The steps of constructing the integrating plasmid, linearizing it, and transforming the yeast host cell are all inherent features of the integration taught by Pearson *et al.* as noted in Stearns *et al.* (see page 287, Fig. 2 legend).

Pearson *et al.* do not teach using the specific genetic marker that is a cycloheximide-resistance gene.

Kondo *et al.* teach using a mutated *C. utilis* L41 protein as a cycloheximide-resistance gene marker in yeast transformation/integration (see Abstract).

It would have been obvious to one of ordinary skill in the art to use a cycloheximide-resistance gene as the generic resistance marker taught by Pearson *et al.* because Pearson *et al.* expressly teach the use of genetic markers and their functional equivalents and Kondo *et al.* identify their sequence as a functional equivalent. One would have been motivated to combine the above references to practice methods using yeast and integrating plasmids containing a cycloheximide-resistance gene because functional equivalents are described as useful variations of the invention of Pearson *et al.* One would have had a reasonable expectation of success that when a cycloheximide-resistance gene was used in the integrating plasmid, successfully transformed yeast host cells would have been cycloheximide resistant and would have produced biotin since the resistance is shown to be effective in *C. utilis* by Kondo *et al.* and since and *C. utilis* naturally produce biotin and introduction of a biotin synthase gene would not have reasonably been expected to inhibit said production.

Other Noteworthy Art

25. The following are cited references or comments on references cited by Applicants for completeness of the record:

a) Applicants cite Kondo *et al.* They teach *C. utilis* rDNA as integration sequences, but not the NsiI-BamHI fragments indicated in Claim 11.

b) Stearns *et al.* teach using HIS3 and URA3 DNA for integration but do not teach *C. utilis* fragments, hence the obviousness rejection above using Rodriguez *et al.*

Allowable Subject Matter

26. The following are the Examiner's comments concerning allowable subject matter present in the pending claims.

Although the specific use of *S. cerevisiae* and *C. utilis* bioB genes are not clear limitations of the pending claims, the Examiner has set forth rejections under 35 U.S.C. § 103(a) in the anticipation that Applicants may also intend to claim these species of methods since these methods are clearly obvious in view of the prior art.

The Examiner also notes that the *C. utilis* art is intervening art prior to the application's filing date but after the foreign priority date. Filing of a certified translation of the priority document would overcome the obviousness art rejection against methods using the *C. utilis* bioB gene.

Conclusion

27. Claims 8-14 are not allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

KMK

July 9, 2003